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(88) Date of publication of the international search report:
19 September 1991 (19.09.91)

(54) Title: TREATMENT OF CONDITIONS AND DISEASE

(57) Abstract

A combination for administration to a mammal which combination employs a therapeutically effective amount of a medicinal and/or therapeutic agent to treat a disease or condition and an amount of hyaluronic acid and/or salts thereof and/or homologues, analogues, derivatives, complexes, esters, fragments and subunits of hyaluronic acid sufficient to facilitate the agent's penetration through the tissue (including scar tissue) at the site to be treated, through the cell membranes into the individual cells to be treated.

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INTERNATIONAL SEARCH REPORT

International Application No PCT/CA 90/00306

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: A 61 K 47/36, 47/20, 31/375, 31/405

II. FIELDS SEARCHED

Minimum Documentation Searched *

Classification System	Classification Symbols
IPC[5]	A 61 K, C 08 L

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched *

III. DOCUMENTS CONSIDERED TO BE RELEVANT *

Category *	Citation of Document, ** with indication, where appropriate, of the relevant passages **	Relevant to Claim No. **
X	EP, A, 0265116 (FIDIA S.p.A.) 27 April 1988 see page 7, line 53 - page 11, line 17 cited in the application	1-10,19-24, 26-39,42-106,108-110 114,176-207 209-216,218 -223,225-241,243,247 248,252-254 258-260,263 264,267-270 273,274
Y	--	40,41,107, 208,242,244

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* Special categories of cited documents: **

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
26th April 1991	23. 05. 91
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Mme. W. van der Drift

International Application No PCT/CA 90/00306

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, ** with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	EP, A, 0197718 (FIDIA S.p.A.) 15 October 1986 see page 2, paragraph 2; page 5, paragraph 2 - page 11, paragraph 3; page 19, formulation 1 - page 21, formulation 7	1-10,19-24, 26-39,42-106,108-110, 114,176-207, 209-216,218-223,225-241, 243,247,248, 252-254,258-260,263,264, 267-270,273, 274
Y	cited in the application	40,41,107, 208,242,244
X	EP, A, 0216453 (FIDIA S.p.A.) 1 April 1987 see page 9, paragraph 2 - page 10, paragraph 4; page 25, paragraph 2 - page 32, paragraph 4	1-10,19-24, 26-39,42-106,108-110, 114,176-207, 209-216,218-223,225-241, 243,247,248, 252-254,258-260,263,264, 267-270,273, 274
Y	cited in the application	40,41,107, 208,242,244
X	EP, A, 0138572 (FIDIA S.p.A.) 24 April 1985 see page 23, paragraph 4 - page 27, paragraph 4; page 38, paragraph 1	1-10,19-24, 26-39,42-106, 108-110,114, 176-207,209-216,218-223, 225-241,243, 247,248,252-254,258-260, 263,264,267-270,273,274
Y	cited in the application	
Y	Chemical Abstracts, vol. 76, no. 10, 6 March 1972, (Columbus, Ohio, US), W.E. Sneader et al.: "Possible mechanism for the action of dimethyl sulfoxide on percutaneous absorption", see page 273, abstract 49897f, & J. Pharm., Pharmacol. 1971, 23(Suppl.) 252S	40,41,107, 208,242,244

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International Application No PCT/CA 90/00306

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, ** with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	EP, A, 0224987 (BIOMATRIX INC.) 10 June 1987 see page 14, example 1; page 23, example 10 --	
A	US, A, 4711780 (FAHIM, M.S.) 8 December 1987 see column 1, line 53 - column 2, line 50; example 6 cited in the application --	
Y	EP, A, 0287210 (MEDICAL RESEARCH INTERNATIONAL LTD) 19 October 1988 see page 2, line 1 - page 3, line 11; - page 3, lines 33-40; page 5, lines 15-20; tables 1-8; claims 1-10	107,208,209, 242,244
A		103-106,176, 206,207,238-241,243
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P,Y	EP, A, 0380367 (STAFFORD-MILLER CONTINENTAL NV-SA) 1 August 1990 see page 2, lines 39-54	107,208,209, 242,244
P,A		103-106,176, 206,207,238-241,243
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Y	Database WPI(L), Derwent 87-337226, & JP, A, 62240628 (KAO CORP.) 21 October 1987 see the whole abstract	107,208,209, 242,244
A		103-106,176, 206,207,238-241,243
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Y	EP, A, 0245126 (MARUHO CO., LTD) 11 November 1987 see claims 1-11	107,208,209, 242,244
A		103-106,176, 206,207,238-241,243

FORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claim numbers * because they relate to subject matter not required to be searched by this Authority, namely:

*Claims searched incompletely: 243, 244

Claims not searched: 11-18,25,111-113,115-175,217,224,245,246, 249-251,255-257,261,262,265,266,271,272.

See PCT rule 39.1 (iv)Method of treatment of the human or animal body by therapy

2. ☐ Claim numbers because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☒ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1.- Claims: 1-10,19-24,26-106,108-110,114,176-207,210-216,218-223, 225-241,243,247,248,252-254,258-260,263,264,267-270,273 274: 107,208,209,242,244 Partially

2. Claims: 107,208,209,242,244 Partially

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. CA 9000306 SA 40056

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 10/07/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A- 0265116	27-04-88	AU-B-	610087	16-05-91
		AU-A-	7960087	21-04-88
		JP-A-	63105003	10-05-88
		US-A-	4957744	18-09-90
		ZA-A-	8707559	13-04-88
EP-A- 0197718	15-10-86	AU-B-	592077	04-01-90
		BE-A-	904547	03-10-86
		CH-A-	672886	15-01-90
		FR-A-	2579895	10-10-86
		JP-A-	61236732	22-10-86
		LU-A-	86386	02-09-86
		US-A-	4736024	05-04-88
EP-A- 0216453	01-04-87	AU-B-	591501	07-12-89
		AU-A-	5983686	26-02-87
		JP-A-	62064802	23-03-87
		US-A-	4965353	23-10-90
		US-A-	4851521	25-07-89
EP-A- 0138572	24-04-85	AU-A-	3414884	18-04-85
		BE-A-	900810	11-04-85
		CA-A-	1205031	27-05-86
		CH-A-	666897	31-08-88
		FR-A-	2553099	12-04-85
		LU-A-	85582	04-06-85
		JP-A-	61028503	08-02-86
EP-A- 0224987	10-06-87	AU-B-	595524	05-04-90
		AU-A-	6090386	04-06-87
		JP-A-	62129226	11-06-87
US-A- 4711780	08-12-87	EP-A-	0314835	10-05-89
EP-A- 0287210	19-10-88	AU-A-	1308988	15-09-88
EP-A- 0380367	01-08-90	AU-A-	4876190	09-08-90
		CA-A-	2008739	27-07-90
		JP-A-	2270815	05-11-90

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. CA 9000306
SA 40056

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 10/07/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0245126	11-11-87	JP-A- 62263122	16-11-87
		US-A- 4873081	10-10-89

DETAILED DISCLOSURE OF THE INVENTION

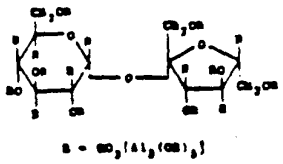
The sulphated saccharide used in accordance with the invention may be a monosaccharide, for instance xylose, fructose or glucose, an oligosaccharide, in particular a disaccharide such as sucrose, lactose, maltose or cellobiose, or a polysaccharide such as dextran, heparan, dermatan, proteodermatan, hyaluronic acid, heparin, chondroitin, amylose, glucosamine, glucosaminoglycan and a mucopolysaccharide or a subunit thereof.

In certain cases, it may be an advantage to use the sulphated saccharide in combination with another wound-healing substance such as a non-sulphated polysaccharide, for instance hyaluronic acid, *vide* Example 3.

The saccharide is preferably a polysulphated or persulphated saccharide, which means that two or more sulphur-containing moieties may be present as substituents on the carbohydrate moiety.

In some cases, the sulphated saccharide may be complexed with or form a salt with a metal, e.g. an alkali or alkaline earth metal such as Na, K, Ca, Sr, Mg or Ba, or Al, Zn, Cu, Ga, Bi and Mn, or with an organic base. The salts are preferably selected from those which are sparingly soluble in water, in order to obtain a slow release effect when they are used topically in the oral cavity. The currently preferred metal is aluminium, optionally in the form of aluminium hydroxide. In the sulphated saccharide, aluminium complexes with the sulphate moiety. Thus, a preferred class of sulphated saccharides is aluminium disaccharide polysulphates of which the currently most preferred substance is sucralfate.

Sucralfate may be represented by the following formula:



The substance may, for instance, be prepared as disclosed in US 3,432,489 by reacting a 1-10% aqueous solution of a disaccharide polysulphate or an alkali metal or alkaline earth metal salt thereof with .. 1-10% aqueous solution containing aluminium ions, preferably $AlCl(OH)_2$ at room temperature and a pH of 4-4.5. The disaccharide polysulphate is prepared by reacting a disaccharide with $ClSO_3H$, H_2SO_4 or H_2SO_4-C_5H_5N.

Sucralfate may also be termed sucrose octakis(hydrogen sulphate) aluminium complex. Its CAS number is 54182-58-0. The commercial product is a white powder which is practically insoluble in water and most organic solvents; it is soluble in acids and alkalis. In practice, there may be slight variations in the chemical composition, for example due to the fact that the sulphation may be slightly incomplete, giving a product that may e.g. contain a certain proportion of molecules which are not octasulphated (persulphated), but which instead are sulphated to a lesser degree, for example heptasulphated. Such minor variations in the commercial product are well known and are reflected in the fact that the aluminium content in commercial products may range from 17 to 21% and the sulphur content from 9.5 to 12.5%. In the present context, the term "sucralfate" also comprises such generally accepted minor variations.

Apart from sulphated saccharides, it is contemplated that other substances may show a similar therapeutic or prophylactic activity in connection with dental diseases and conditions as defined above. Examples of such substances are ketotifen and chromoglycate and other

antiallergic agents known to act on and stabilize cell surfaces, such agents also being suspected of inhibiting the activity of hyaluronidase.

Although there may be cases where the sulphated saccharide may be administered as such, it will typically be compounded with one or more pharmaceutically acceptable carriers or excipients to be presented in a form which is suitable for topical application to teeth or tooth-supporting tissue. It will usually be in the form of a fluid, semi-fluid, semi-solid or solid preparation such as a solution, suspension, powder, paste, gel, cream, salve, dental fixative, periodontal implant, chewing gum, chewable tablet, effervescent tablet or lozenge.

The topical preparation may be formulated in accordance with conventional pharmaceutical practice with pharmaceutical excipients conventionally used for topical applications such as alginate, pectin, gelatin and derivatives thereof, cellulose derivatives such as methyl cellulose, carboxymethyl cellulose or oxidised cellulose, guar gum, acacia gum, karaya gum, tragacanth gum, locust bean gum, bentonite, agar, carbomer, bladderwrack, ceratonia, dextran and derivatives thereof, ghatti gum, hectorite, ispaghula husk, polyvinylpyrrolidone, silica and derivatives thereof, such as silicates, xanthan gum, kaolin, chalk, dicalcium phosphate, alumina, pyrophosphate, talc, starch and derivatives thereof, paraffin, water, vegetable and animal oils, isopropyl myristate, polyethylene, polyethylene oxide, polyethylene glycol and polyethylene glycol esters, polypropylene glycol, glycerol, ethanol, propanol, propylene glycol, glycols, alcohols, fatty alcohols, fixed oils, sodium, potassium, aluminium, magnesium or calcium salts (such as the chloride, carbonate, bicarbonate, citrate, gluconate, lactate, acetate, gluceptate or tartrate), rubbers (artifical or natural) such as chicle, polyisobutylene, etc., sorbitane esters, quaternary ammonium salts, salts of fatty acids and polysorbates.

The preparation of the invention may also contain conventional additives such as thickeners, emulsifiers, anionic, cationic and

non-ionic surfactants, stabilizing agents, preservatives, abrasives, flavouring agents, etc.

It has surprisingly been found that a preparation which is particularly effective for prophylactic purposes may be prepared by mixing the sulphated saccharide with a toothpaste preparation. The sulphated saccharide has been found to be compatible with toothpaste preparations of the type commonly available as commercial toothpastes, and can thus be used on a regular basis for the prevention of e.g. inflammatory and plaque-related conditions.

A toothpaste will usually contain polishing agents, surfactants, gelling agents and other excipients such as flavouring and colouring agents. The polishing agent may be selected from those which are currently employed for this purpose in dental preparations. Suitable examples are water-insoluble sodium or potassium metaphosphate, hydrated or anhydrous dicalcium phosphate, calcium pyrophosphate, zirconium silicate or mixtures thereof. Particularly useful polishing agents are various forms of silica, especially silica xerogels such as are described in U.S. patent No. 3,538,230. The polishing agent is generally finely divided, with a particle size smaller than 10 μm, for example 2-6 μm. The polishing agent may be employed in an amount of 10-99% by weight of the toothpaste. Typically the toothpaste preparations will contain 20-75% of the polishing agent.

A suitable surfactant is normally included in the toothpaste preparations. The surfactant is typically a water-soluble non-soap synthetic organic detergent. Suitable detergents are the water-soluble salts of: higher fatty acid monoglyceride monosulphates (for example sodium hydrogenated coconut fatty acid monoglyceride monosulphate); higher alkyl sulphates (for example sodium lauryl sulphate); alkylaryl-sulphonates (for example sodium dodecylbenzene-sulphonates); and higher alkyl sulphoacetates (for example sodium lauryl sulphoacetate). In addition, there may be employed saturated higher aliphatic acyl amides of lower aliphatic amino carboxylic acids having 12-16 carbon atoms in the acyl radical and in which the amino acid portion is derived from the lower aliphatic saturated monoaminocarboxylic acids having 2-6 carbon atoms, such as fatty acid amides of glycine.

sarcosine, alanine, 3-aminopropanoic acid and valine, in particular the N-lauryl, myristoyl and palmitoyl sarcosinate compounds. Conventional non-ionic surfactants may also be included if desired.

The surface active materials are generally present in an amount of about 0.05-10%, typically about 0.5-5%, by weight of the toothpaste preparation.

Typically the liquids of the toothpaste will comprise mainly water, glycerol, sorbitol, propylene glycol or mixtures thereof. An advantageous mixture is water and glycerol, preferably with sorbitol. A gelling agent such as natural or synthetic gums and gum-like materials, e.g. Irish Moss or sodium carboxymethylcellulose, may be used. Other gums which may be used are gum tragacanth, polyvinyl-pyrrolidone and starch. They are usually used in an amount up to about 10%, typically about 0.5-5%, by weight of the toothpaste.

The pH of a toothpaste is substantially neutral, such as a pH of about 6-8. If desired, a small amount of a pH-regulating agent, e.g. a small amount of an acid such as citric acid or an alkaline material may be added.

The toothpaste may also contain other materials such as soluble saccharin, flavouring oils (e.g. oils of spearmint, peppermint, wintergreen), colouring or whitening agents (e.g. titanium dioxide), preservatives (e.g. sodium benzoate), emulsifying agents, silicones, alcohol, menthol and chlorophyll compounds (e.g. sodium copper chlorophyllin).

The content of sucralfate or other sulphated saccharide in the toothpaste of the above type or types discussed below will normally be in the range of 1-20% by weight, calculated on the weight of the total toothpaste composition, such as in the range of 5-20% by weight, in particular about 10-20% by weight such as 12-18% by weight. The latter ranges are especially indicated for toothpastes which are used for treatment of gingivitis and periodontosis. It is, however, also interesting to provide toothpastes having a lower content of sucralfate which will often predominantly be adapted for preventive or

prophylactic purposes. For such purposes, sucralfate content ranges from about 0.1 to about 5% by weight may be interesting.

A special type of toothpaste are toothpastes which are substantially clear gels. Such toothpastes may either contain no polishing agents at all or may contain the polishing agent in such finely divided form that the gels will still appear substantially clear. Such gel toothpaste types may either be used *per se* or may be combined with toothpastes containing polishing agents as discussed above.

There are, of course, numerous examples of special toothpastes or dentifrices adapted for special purposes or with special advantages. Thus, e.g., EP 280077 describes a toothpaste which contains stabilized dicalcium phosphate dihydrate, resulting in a high water absorption capacity and an adequate viscosity at low abrasive content; US 4,618,488 discloses stable toothpastes, in particular transparent toothpastes, which contain amourphous silica and/or silicate abrasive with specific surface areas, resulting in long term stability of the transparency of the toothpaste; US 4,632,826 discloses a toothpaste, the polishing agent of which is constituted by a combination of silicagel and/or precipitated silica and weakly calcined alumina mixture, resulting in a toothpaste with low scratching and abrasion effect and with high storage stability; US 4,721,614 discloses a toothpaste which contains sodium bicarbonate as sole abrasive, thus avoiding excessive abrasive properties and retaining a good storage stability; US 4,702,905 and US 4,716,034 disclose toothpastes which are resistent to syneresis in contact with polyolefin packaging, which toothpastes are thus suitable for packaging in e.g. laminate tubes, mechanical dispensers and flexible sachets; US 4,599,363 discloses a method for wetting and dispersing powders for toothpaste preparations in turbulent liquid medium, the method preventing formation of lumps and loss of powdered solids and resulting in high quality toothpaste compositions; US 4,701,319 discloses a toothpaste which has good stability, viscocity and processing properties, the toothpaste containing abrasive, carboxyvinyl polymer, and a carrageenan humectant.